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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,711	BAKER ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Decision on Petition (mailed 18 April 2006) is noted. Accordingly, Applicant's request for reconsideration of the finality of the rejection of the last Office action is granted, and finality is withdrawn. The Examiner's Answer mailed 11 January 2006 is now designated a non-final office action, in accordance with the Decision on Petition of 18 April 2006. The Reply Brief received 09 March 2006 and the Supplemental Response received 25 September 2006 are being treated as responses to a non-final office action, in accordance with the Decision on Petition.

The Information Disclosure Statement of 25 September 2006 has been received and considered. The second declaration of Dr. Polakis, received 25 September 2006, has also been entered and considered.

Claims 1-118 and 124 are canceled. Claims 119-123 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 119-123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for reasons of record.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific

and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record.

Applicant has submitted arguments in two responses, which will be addressed in turn:

1. Applicant's arguments submitted in the Reply Brief received 09 March 2006 have been fully considered but are not found to be persuasive for the following reasons.

Applicant argues that the rejection uses a legally incorrect standard in requiring that a positive result be shown for most or a larger percentage of the tissue samples studied. Applicant urges that such a requirement is the domain of the FDA, not the USPTO. Applicant argues that the identification of a pharmacologic or diagnostic utility is legally sufficient. Applicant argues hat some tumor markers are useful for identifying rare malignancies, and have great value in tumor diagnosis and prognosis. This has been fully considered but is not found to be persuasive. In the instant case, the claims are directed to antibodies that bind polypeptides. The specification asserts that PRO341 polypeptides are elevated in tumor tissues based on gene amplification results; however, the literature evidences that this assumption is a false one. Regarding rare tumor markers, such rare tumor markers are only useful if the type of rare tumor it identifies is known. The specification has not identified anything rare, or anything in common, among the three lung tumor samples in which the PRO341 gene is amplified. PRO341 gene tested positive in LT16, LT17, and LT21 samples. Table 8 (p. 546)

identifies these samples as lung squamous cell carcinoma stage IB, lung squamous cell carcinoma stage IIB, and lung large cell carcinoma stage IIB.

Applicant criticizes the Pennica and Konopka references. These arguments are largely cumulative of those previously made of record and addressed by the examiner. Thus, the arguments are not persuasive for reasons of record.

Similarly, Applicant relies again on Orntoft et al., Hyman et al., and Pollack et al. Again, these arguments are not found to be persuasive for reasons of record.

Applicant addresses the Hu et al., Haynes et al., LeBaer, Gygi et al., Chen et al., Lian et al., Fessler et al., and Greenbaum et al. publications beginning at p. 11 of the Reply Brief. Applicant indicates that the Hu et al. and LeBaer publications report statistical analysis using literature mining and, as such, do not support lack of utility. This has been fully considered but is not found to be persuasive because Hu et al. and LeBaer provide conclusions based on many research efforts. If anything, their conclusions are even more probative than those based on a smaller study. Furthermore, the instant specification provides no statistical analysis.

Applicant's criticisms of Haynes et al. have already been addressed on the record.

Applicant argues that Gygi et al. is mischaracterized in the Examiner's Answer, and asserts that Gygi et al. report a general trend of correlation between mRNA and protein levels. This has been fully considered but is not found to be persuasive because Gygi et al. state,

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from

> quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient."

Applicant argues that the Chen et al. publication is not applicable to the instant application because the 2D gels used by Chen et al. exclude key regulatory proteins, an analyze the data in a different manner than the instant application. Applicant urges that Chen et al. show that it is more likely than not that increased mRNA expression correlates well with increased protein expression. This has been fully considered but is not found to be persuasive. Chen et al. compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312).

Applicant refers to a later paper by the Chen et al. authors. However, this paper was not submitted, and is thus not found to be persuasive.

Applicant states that the utility rejection is based upon a misrepresentation of the data presented in the Haynes et al., Gygi et al., and Chen et al. references. This has been fully considered but is not found to be persuasive for the reasons of record.

Applicant's criticism of Hanna and Mornin have already been addressed on the record.

Applicant argues that the Lian et al. publication is limited to differentiating myeloid cells and does not teach anything regarding a lack of correlation between mRNA levels and protein levels in general. Applicant also finds fault with Lian et al. for using a relatively insensitive assay. This has been fully considered but is not found to be persuasive. Lian et al. show a lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels.")

Applicant takes issue with the Fessler et al. publication, stating that Fessler et al. is limited to studying a few proteins/RNAs and using an insensitive assay. This has been fully considered but is not found to be persuasive because Fessler et al. found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

Applciatn takes issue wth the Greenbaum et al. publication beginning at p. 18. Applicant argues that Greenbaum et al. is limited to yeast and that they find a high level of correlation between mRNA and protein expression. This has been fully considered but is not found to be persuasive. Greenbaum et al. clearly caution against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited

protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells and, for the most part, they have reported only minimal and/or limited correlations. It is also clear from this section that Greenbaum et al. considered correlations in human cancer studies, not only yeast.

Applicant argues that the examiner's comments regarding the commercial success of gene chips supports Applciant's position that it is more likely than not that those skilled in the art expect that it is more likely than not that mRNA levels are predictive of protein levels. This has been fully considered but is not found to be persuasive. Since the chips contain many sequences and can be processed automatically, the skilled artisan may think it worthwhile to screen it even if only a few show correlation.

Applciant points to the Polakis delcataion, but this has already been addressed on the record.

2. Applicant's additional arguments provided in the supplemental response received 25 September 2006 have been fully considered but are not found to be persuasive for the following reasons.

As a preliminary matter, it is noted that the response refers to PRO343. It is elieved that this is a typographical error since the instant claims are directed to antibodies that bind PRO341. Confirmation is requested.

Applicant discusses the Polakis I declaration. This was discussed in the examiner's answer:

> In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO341 (i.e., data regarding amplification of PRO341 genomic DNA), and does not disclose any information regarding PRO341 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicant presents and discusses a second declaration by Dr. Polakis, submitted with the response on 25 September 2006. Applicant argues that this declaration provides the facts, set forth in a table (Exhibit B), for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR § 1.132 filed 25 September 2006 is insufficient to overcome the rejection of claims 119-123 based upon 25 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. Specifically, data for PRO341 does not appear in the table (Exhibit B). Furthermore, it is not clear how the clones appearing in the table compare to PRO451, or if the results presented in the table were determined by the same methodology as presented in Example 30 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g., microarray, Northern blot, quantitative PCR? Was the "universal normal control" used or were matched tissue controls used? The declaration only states that levels of mRNA and protein in tumor tissue were compared to normal tissue.

Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc.). Applicant asserts that changes in mRNA level

generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following: "The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription." However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation

machinery (see pages 973-974). Celis et al. also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2).

Furthermore, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner) and Nagaraja et al. (2006), Waghray et al. (2001) and Sagynaliev et al. (2006) (described below).

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one. Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Orntoft et al. concentrated on

regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO341 in the instant specification. That is, it is not clear whether or not PRO341 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear.

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated. Nagaraja et al. (Oncogene, 25:2328-2338, 2006) characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and vice versa" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068). In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that changes in mRNA expression frequently do not result in changes in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO341. The specification simply discloses a static measurement of PRO341 mRNA in lung tumor as compared to a universal control.

There are no teachings in the specification as to the differential expression of PRO341 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO341 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

The state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. Lilley et al. teach that "DNA chips (mRNA profiling studies) can contribute to the study of gene expression in response to a particular biological perturbation. However, the extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made" ("Proteomics" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, page 351). Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pages 269-286, especially pg 283). King et al. disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al. state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2; see also Bork et al., Genome Res 398-400, 2000, especially pg 398, bottom of col 3). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA

expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Madoz-Gurpide et al. disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (pg 53, 1st full paragraph). However, the specification of the instant application has only disclosed that the PRO341 polynucleotide is overexpressed in lung tumor. The specification does not indicate that the PRO341 polypeptide has been overexpressed in the lung tumor sample tested. Given the asserted increase in PRO341 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the purported increase in PRO341 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
"a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO341 polypeptides have utility in the fields of cancer diagnostics is not substantial.

Additionally, the majority of the newly cited references by Applicants are drawn to genes known or suspected to be over expressed or under expressed in cancers, and that are involved with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the protein is important in the development and progression of the cancer. For example, Wang et al. analyzes expression of the cadherins, which are a family of transmembrane proteins that play a crucial role in cell differentiation, cell migration, and intercellular adhesion. Down-regulation of E-cadherin protein had been shown in various human cancers. Wang et al. states: "In conclusion, this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied. This down-regulation may play an important role in the pathogenesis of prostate cancer." Maruyama et al. studied the expression of Id proteins. Id proteins antagonize basic helix-loop-helix proteins, inhibit differentiation, and enhance cell proliferation. In their study they compared the expression of Id-I, Id-2, and Id-3 in the normal pancreas, in pancreatic cancer, and in chronic pancreatitis (CP), and found increases in both mRNA and protein compared to normal. Maruyama et al. state: "These findings suggest that increased Id expression may be associated with enhanced proliferative potential of pancreatic cancer cells and of proliferating or dysplastic ductal cells in CP." Munaut et al. teach that vascular endothelial growth factor (VEGF) is the major endothelial mitogen in central nervous system neoplasms and it is expressed in 64-95%

of glioblastomas (GBMs). Munaut et al. state "Tumour cells are the main source of VEGF in GBMs whereas VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial ceils. Infiltrating tumour cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinase's (MMPs). Recent studies have shown that VEGF expression and bioavailability can be modulated by MMPs. We reported previously that the expression of MTI-MMP in human breast cancer cells was associated with an enhanced VEGF expression.....Our results suggest that the interplay between metalloproteinase's and VEGF previously described in experimental tumours may also be operative in human GBMs. Because of its dual ability to activate MMP-2 and. to up-regulate VEGF, MTI-MMP might be of central importance in the growth of GBMs and represent an interesting target for anti-cancer treatments."

Rudlowski et al. (cited in IDS filed 25 September 2006), examined GLUT1 mRNA and protein induction in malignant transformation of cervical cancer. The authors state: "We studied whether induction of glucose transporters (GLUTs) 1 to 4 correlates with human papillomavirus (HPV)-dependent malignant transformation of cervical epithelium. Tissue samples of cervical intraepithelial neoplasia (CIN; grades 1 to 3), invasive carcinomas, and lymph node metastasis were examined. HPV typing was performed. In CIN 3 high-risk HPV lesions, cervical cancer, and metastasis, GLUT1 was expressed at highest levels with a strong correlation of GLUT1 mRNA and protein expression. Immunostains for GLUT2 to GLUT4 were negative. Cervical tumour cells respond to enhanced glucose utilization by up-regulation of GLUTI. The strong induction of GLUTI

mRNA and protein in HPV-positive CIN 3 lesions suggests GLUTI over expression as an early event in cervical neoplasia. GLUTI is potentially relevant as a diagnostic tool and glucose metabolism as a therapeutic target in cervical cancer. "

Bea et al. (cited in IDS filed 25 September 2006) studied gene amplification, mRNA expression and protein expression of the BMI-1 gene, which is a putative oncogene belonging to the Polycomb group family that cooperates with c-myc in the generation of mouse lymphomas and seems to participate in cell cycle regulation and senescence by acting as a transcriptional repressor of the INK4a/AILF locus. Bea et al. reported that four tumours with gene amplification showed significantly higher mRNA levels and significantly higher protein expression than other MCLs and NHLs with the BMI-1 germ line configuration. Applicants assert that Bea et al. supports the assertion that gene amplification is correlated with both increased mRNA and protein expression. However, as discussed above, it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased protein expression. PRO341 is not a putative oncogene, and the function of the encoded protein is not known.

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification, a single reference, that by Godbout, is pertinent to the issue at hand. Far from teaching predictability for expression of PRO341 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN

in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons."

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO341 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO341 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any

other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO341.

In summary, of applicants' 149 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO341 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*."

In view of the preponderance of the totality of the evidence, the rejections are deemed proper and are maintained.

Conclusion

No claims are allowed.

The Examiner's Answer mailed 12 October 2005 is now designated a non-final office action, in accordance with the Decision on Petition of 30 January 2006. Therefore, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant is advised that the instant rejection was made final because the same claims were maintained as rejected on the same grounds that have been of record. However, new references have been cited as evidence supporting the rejections of record. Applicant may submit counter-evidence in response to this office action, which will be appropriately entered after final. Alternatively, Applicant may wish to submit an Appeal Brief in response to this office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER